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The interleukin-17 cytokine family: critical players in host defence and inflammatory diseases

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Summary

The interleukin-17 (IL-17) cytokines, IL-17A to IL-17F, are emerging as critical players in host defence responses and inflammatory diseases. Substantial data support the role of these proteins in innate and adaptive immunity. Of these family members, IL-17A, IL-17F and IL-17E have been the best studied. Both IL-17A and IL-17F contribute to the host response to extracellular bacteria and fungi, and IL-17E has been shown to play a role in parasitic infections. In addition, numerous pre-clinical and clinical studies link these proteins to the pathogenesis of inflammatory diseases, and a number of therapeutic programmes targeting these family members are in clinical development. This review will highlight the cellular sources, receptors/target cells, and role in inflammation of these and the less-characterized family members, IL-17B, IL-17C and IL-17D.

Keywords: autoimmunity; cytokines; host defence; interleukin-17 receptors; inflammation

Introduction

The interleukin-17 (IL-17) cytokines are emerging as key players in immune responses. The first member to be identified, IL-17A, was originally cloned as cytotoxic T-lymphocyte antigen-8, a gene sharing homology with the HSV13 gene from herpesvirus Saimiri.[1] Seminal work by Yao *et al.*[2] identified this gene as a cytokine, initially designated as IL-17, and most recently as IL-17A, the prototypic member of this family. The other members, IL-17B to IL-17F were subsequently identified based on their homology to IL-17A (Fig. 1).[3] These proteins are highly conserved at the C terminus, and contain five spatially conserved cysteine residues that mediate dimerization.[4] Members of the IL-17 receptor family, IL-17RA to IL-17RE, mediate the biological functions of these cytokines.[3] Accumulating evidence indicates that these interactions induce pro-inflammatory programmes.[3]

IL-17A and IL-17F

Interleukin-17A and IL-17F are 50% identical, and consequently share many biological properties (Fig. 1). Both cytokines are secreted as disulphide linked homodimers. In addition, a heterodimeric species consisting of disulphide-linked IL-17A and IL-17F has also been identified.[5,6] These proteins signal through a heterodimeric receptor complex consisting of the IL-17RA and IL-17RC chains, which is detected on a number of cells (Table 2).[3,7–9] Although these dimers stimulate many overlapping pathways, the degree of induction varies between the species, with the IL-17A homodimer promoting more robust responses than the heterodimer or the IL-17F homodimer.[5,6,10,11]

Multiple cell types express IL-17A and IL-17F (Table 1).[3,5,6,10,12] Much effort has been placed on understanding the biology of the $CD4^+$ T helper type 17 (Th17) subset, which is the predominant cell-type to produce IL-17A and IL-17F. The Th17 cells are critical to the adaptive immune response against bacterial and fungal infections, and also contribute to the pathogenesis of several inflammatory diseases.[13] Differentiation of this subset from naive $CD4^+$ T cells is dependent on signals from IL-6 and transforming growth factor-β, while maintenance of this lineage requires IL-23 and IL-21.[14–22] Interestingly, a recent study by Ghoreschi *et al.*[23] shows that pathogenic Th17 cells can also be generated in a transforming growth factor-β-independent manner. Understanding how these

Abbreviations: EAE, experimental autoimmune encephalomyelitis; IBD, inflammatory bowel disease; IL-17, interleukin-17; IL-17R, interleukin-17; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NKT, natural killer T; RA, rheumatoid arthritis; Th17, T helper type 17; TNF-α, tumour necrosis factor-α.

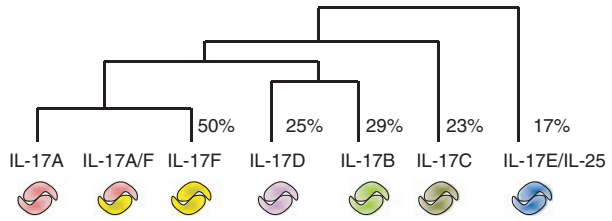

Figure 1. Homology of interleukin-17 (IL-17) family members to IL-17A. The dendrogram indicates the percentage homology between each of the IL-17 family members and IL-17A. IL-17F shares greater homology with IL-17A, whereas other family members are more divergent. Percentages reflect both mouse and human IL-17 family members.

Table 1. Cellular sources of interleukin-17 family members

	Cell type	References
IL-17A	Th17	3,5,6,10
	LTi	12
	NK	12
	iNKT	12
	Mast cells	12
	Neutrophils	12
	$\gamma\delta$ T cells	12
IL-17B	Chondrocytes	83,85–87
	Neurons	84
IL-17C	Epithelial cells	9,88
IL-17D	Undefined	
IL-17E	Memory Th2	64
	Eosinophils	64
	Basophils	64
	Mast cells	63
	Epithelial cells	62,65
IL-17F	Th17	3,5,6,10
	LTi	12
	NK	12
	iNKT	12
	Neutrophils	12
	$\gamma\delta$ T cells	12

iNK, invariant natural killer; LTi, lymphoid tissue inducer-like cells; NK, natural killer; Th17, T hlper type 17.

different cytokine combinations contribute to the generation of Th17 cells during inflammation is an area of active research. In addition to cytokines, commensal bacteria also induce Th17 cells.[24] Segmented filamentous bacteria are potent inducers of Th17 cells in the lamina propria of the small intestine, and antibiotic-mediated depletion of these bacteria inhibits Th17 differentiation.[25] These stimuli activate a number of transcription factors to up-regulate the *il17a* and *il17f* genes.[22]

Innate immune cells also contribute to the generation of IL-17A and IL-17F.[12] Lymphoid tissue inducer-like cells, $\gamma\delta$ T cells, invariant natural killer T (iNKT) cells and NKT cells secrete IL-17A in response to IL-23 and bacterial products.[12] Given the proximity of these cells to mucosal barriers, the ability to generate IL-17A and IL-17F in response to these stimuli may provide the first line of defence against microbial infections.

Table 2. Expression of interleukin-17 receptors

	Cell type	References
IL-17RA	Ubiquitous	3,7–9
IL-17RB	ckit$^+$lin$^-$	62,71–73
	T helper type 9	74
	Fibroblasts	75
	T helper type 2	62
	Basophils	59,62
IL-17RC	Adipocytes	3,7,8
	Chondrocytes	3,7
	Fibroblasts	3
	Epithelial cells	7,9
IL-17RD	Epithelial cells	113
	Endothelial cells	113
IL-17RE	Undefined	

Interleukin-17A and IL-17F promote tissue-mediated innate immunity by triggering pro-inflammatory responses. These downstream targets can be divided into pro-inflammatory chemokines (CXCL1, CXCL8, CXC L10), cytokines [tumour necrosis factor-α (TNF-α), IL-1, IL-6, and granulocyte–macrophage and granulocyte colony-stimulating factors], anti-microbial peptides (mucins, β-defensins, S100A7-9), and tissue remodelling and acute-phase responses (SAA, MMP1, RANKL).[26] Furthermore, the combined action of IL-17A or IL-17F with other cytokines such as TNF-α, IL-1β and interferon-γ synergistically augments the induction of pro-inflammatory responses from various target cells.[27–29] As both IL-17A and IL-17F regulate neutrophil mobilization by promoting granulopoiesis, inflammation is observed when either cytokine is over-expressed *in vivo*.[26,30–33]

In vivo studies substantiate the importance of these cytokines in anti-microbial responses. Host defence pathways are impaired in mice that are deficient in either or both cytokines. Infection of *il17a*$^{-/-}$, *il17f*$^{-/-}$ and *il17a*$^{-/-}$:*il17f*$^{-/-}$ mice with either *Citrobacter rodentium* or *Staphylococcus aureus* resulted in increased bacterial burden and pathology, signifying the requirement of these cytokines in defence against Gram-negative and Gram-positive bacteria.[34,35] Clearance of the pulmonary pathogen *Klebsiella pneumoniae* was also defective in *il17a*$^{-/-}$ mice.[35] Theses phenotypes are attributed to defective granulocyte colony-stimulating factor responses, granulopoiesis, and neutrophil mobilization.[35,36] Additional infection models reveal the importance of this pathway in anti-fungal immunity. Neutralizing IL-17A with a blocking antibody increases fungal burden in a model of *Pneumocystis carinii* infection, while over-expressing IL-17A using an adenoviral

system protects mice infected with lethal doses of *Candida albicans*.[37,38] Interleukin-17A also plays a role in immunity to intracellular bacteria. However, *il17a*$^{-/-}$ mice are not susceptible to primary infections with intracellular bacterial pathogens such as *Mycobacterium tuberculosis* and *Listeria monocytogenes,* which require Th1 immunity for eradication. Instead, IL-17A is critical for the enhancement of memory responses against these pathogens.[35] Collectively, these studies demonstrate the importance of these cytokines in host defence against bacteria and fungi.

Although these proteins play a protective role in host defence, excessive activation of this pathway contributes to autoimmunity.[13] Both IL-17A and IL-17F are elevated in multiple human autoimmune diseases (Table 3).[9,34,39–46] Pre-clinical models of rheumatoid arthritis (RA), multiple sclerosis (MS) and inflammatory bowel disease (IBD) suggest that these proteins participate in disease pathogenesis, but the contribution of each cytokine to the development of disease varies, with IL-17A playing a more dominant role in RA and MS, whereas IL-17F is more important in IBD.[30,34,47] Expression of IL-17A in the knee joint of mice with collagen-induced arthritis exacerbated joint destruction and disease progression, whereas the absence of IL-17A reduced disease activity in pre-clinical models of RA.[47–49] In contrast, analysis of *Il17f*$^{-/-}$ suggests that this cytokine has a non-essential role in the development of arthritis, despite displaying similar pro-inflammatory properties as IL-17A in cultured RA synoviocytes.[34,46] Likewise, the clinical symptoms of experimental autoimmune encephalomyelitis (EAE), a murine model for MS, are reduced in *il17a*$^{-/-}$ mice and in mice treated with an anti-IL-17A blocking antibody.[30,33,50,51] Conversely, akin to what was observed in the arthritis pre-clinical models, moderate improvement in recovery from EAE is seen in *Il17f*$^{-/-}$ mice.[30] Interestingly, the detection of elevated levels of IL-17F in human MS patients unresponsive to interferon-β, suggests that IL-17F may play a more dominant role in inflammation than that predicted by the mouse system.[52] Further investigation is required to understand the role of IL-17F in MS.

Table 3. Interleukin-17 (IL-17) family cytokines and receptors in human disease

	Disease	Expression	References
IL-17A	RA	Elevated	46,89
	IBD	Elevated	40
	Psoriasis	Elevated	9,42,44
	MS	Elevated	41
	Atherosclerosis	Elevated	55
IL-17B	Psoriasis	Reduced	9
IL-17C	Psoriasis	Elevated	9
IL-17D	Psoriasis	Reduced	9
IL-17E	Asthma	Elevated	64,75
	Atopic dermatitis	Elevated	64
	IBD	Reduced	79
IL-17F	RA	Elevated	94–96
	IBD	Elevated	43
	Psoriasis	Elevated	9,42
IL-17RA	RA	Elevated	94,95
	IBD	Elevated	96
IL-17RB	Asthma	Elevated	64,107
	Atopic dermatitis	Elevated	64
IL-17RC	RA	Elevated	95

IBD, inflammatory bowel disease; MS, multiple sclerosis; RA, rheumatoid arthritis.

The contribution of IL-17A and IL-17F to IBD is unclear, as pre-clinical models have yielded inconsistent results. Studies using the dextran-sulphate-sodium-induced colitis model suggest that IL-17A has a protective role in the gut. Neutralization of IL-17A or genetic deficiency of *il17a* exacerbated disease in this model.[30,53] However, dextran-sulphate-sodium-treated *il17f*$^{-/-}$ mice displayed reduced colitis.[30] Conflicting results were observed using a second model of IBD, the CD45RB^{hi} transfer model of colitis. One report corroborates a protective role for IL-17A whereas the other suggests that IL-17A and IL-17F are pathogenic in this model.[53,54] Additional studies are needed to resolve this discrepancy, in particular, understanding how the intestinal microflora shape Th17 cell differentiation and secretion of IL-17A and IL-17F is necessary to understand the biology of these molecules in homeostatic and disease states.

Interleukin-17A has also been implicated in inflammation associated with metabolic diseases. It is detected in T cells from specimens of coronary atherosclerosis, and patients with acute coronary syndrome display elevated levels of circulating Th17 cells and cytokines.[55] Blockade of IL-17A decreases lesion size, lipid accumulation and cellular infiltration in the *apoE*$^{-/-}$ models of atherosclerosis. Similarly, *il17a*$^{-/-}$ mice fed a high-fat diet also develop fewer atherosclerotic lesions. Likewise, glucose homeostasis is impaired in *il17a*$^{-/-}$ mice, an effect attributed to IL-17A signalling in adipocytes.[8] How IL-17A contributes to human atherosclerosis remains to be determined.

The pre-clinical and clinical data substantiate a key role for IL-17A/F in host defence and inflammatory diseases, and rationalize the development of therapeutics to target this pathway. Multiple programmes targeting different aspects of the IL-17 pathway are in clinical development.[56] Recent reports from Novartis and Eli Lilly indicate that neutralization of IL-17A has therapeutic benefit in autoimmune diseases. The efficacy and safety of the Novartis molecule, AIN457, were investigated in phase I/IIa trials in patients with psoriasis, RA or autoimmune uveitis.[57] Significant reductions in disease activity were observed in patients with psoriasis or RA treated with AIN457. In addition, positive responses to AIN457 were

observed in a proportion of uveitis patients. Likewise, patients with RA treated with the Lilly drug, LY2439821, also displayed improvements in the disease activity score DAS28 and American College of Rheumatology core set parameters.[58] Further studies are needed to assess the long-term efficacy of these therapies in these diseases and other inflammatory disorders.

IL-17E (IL-25)

Interleukin-17E, or IL-25, is the most divergent cytokine in the IL-17 family, sharing only 25–35% homology with the other members (Fig. 1). Basal *il17e* RNA is broadly expressed and can be augmented by allergens and infectious agents.[59–62] Inoculation of mice with the intestinal nematode *Nippostrongylus brasiliensis,* promotes IL-17E expression in the gastrointestinal tract, while exposure to *Aspergillus fumigatus*, protease allergens, or ovalbumin sensitization increases IL-17E expression in the lung.[31] Multiple sources of IL-17E have been described (Table 1).[59,62–65]

A combination of biochemical and genetic studies reveal that IL-17E uses a heterodimeric complex consisting of IL-17RA and IL-17RB (alternatively known as IL-17Rh1, IL-17BR, IL-25R, or Evi27) for activity. Surface plasmon resonance analyses revealed that IL-17RB binds to IL-17E with high affinity.[4] Although a direct physical interaction between IL-17E and IL-17RA has not been detected, association of IL-17RA with a pre-formed IL-17E–IL-17RB complex was reported in the micromolar range.[66]

In vivo studies indicate that IL-17E participates in the Th2 immune response. Transgenic mice expressing IL-17E under a liver-specific or myosin promoter display eosinophilia and neutrophilia in the blood, and enhance serum IgE, IgA, IgG1 and Th2 cytokines.[60,67] Similar results were observed in the bronchoalveolar lavage fluid from mice expressing IL-17E under a lung-specific promoter.[68] Analyses of *il17e*$^{-/-}$ mice revealed the necessity for this cytokine in the clearance of the *Trichuris muris* and *N. brasiliensis* worms, both pathogens requiring Th2 immunity for eradication.[69,70] In agreement with the genetic data, *N. brasiliensis* is rapidly cleared upon *in vivo* administration of IL-17E.[69]

Initial efforts to characterize the IL-17E target cells responsible for Th2 immunity focused on using RNA and protein analyses to identify IL-17RB^{+} populations. These studies revealed expression of IL-17RB on haematopoietic and non-haematopoietic populations (Table 2).[59,64] However, understanding whether these cells represented true IL-17E targets and how these cell-types participate in IL-17E biology remained unclear. A major breakthrough in the field came recently when several groups successfully isolated individual populations of cells and demonstrated both IL-17E responsiveness and dependence on functional IL-17RB and IL-17RA. The use of murine reporter strains for Th2 cytokines and a spectrum of lineage markers enabled the characterization of the ckit^{+} lin^{-} IL-17E-responsive cells.[71–73] Administration of recombinant IL-17E to IL-13 or IL-4 e-GFP reporter mice resulted in a robust expansion of these cells, primarily in the gastrointestinal tract, lymph nodes and spleen, with little detection in the bone marrow or blood. In addition, expansion of this population is detected following *N. brasiliensis* infection of wild-type mice, but not in *il17ra*$^{-/-}$, *il17rb*$^{-/-}$, or in mice treated with anti-IL-17E blocking antibody, demonstrating the requirement for intact IL-17E signalling in these cells.[72] Microarray analysis reveals that they induce a distinct gene expression pattern from basophils and Th2 cells.[73] Neill *et al.*[71] demonstrated that this population is also responsive to IL-33, and the combination of IL-17E and IL-33 is required for efficient expulsion of the nematode *N. brasiliensis*. Wild-type ckit^{+} lin^{-} cells are sufficient to provide Th2 immunity during parasitic infection. Adoptive transfer of these cells rescues the defects in worm clearance seen in the *il17rb*$^{-/-}$, *il17rb*$^{-/-}$: *st2*$^{-/-}$ and the *il4*$^{-/-}$*:il13*$^{-/-}$ infected with *N. brasiliensis*, and in the *il17e*$^{-/-}$ strain infected with *Trichuris muris*.[71,72] Furthermore, *in vitro* differentiation studies suggest that this population has multi-pluripotent potential and can give rise to mast cells, basophils and macrophages.[72]

The Th9 subset was also identified as targets of IL-17E.[74] T helper type 9 cells express both IL-17RA and IL-17RB and secrete IL-9 in response to IL-17E. It is suggested that IL-9 participates in allergic inflammation. Allergen challenge in *il17e*$^{-/-}$ mice resulted in decreased IL-9, IL-4, IL-5 and IL-13 expression, which was accompanied by reduced disease. However, the specific roles of IL-9 versus the conventional Th2 cytokines in this model are unclear.

Consistent with a role in Th2 immunity, IL-17E is implicated in the pathogenesis of allergic inflammation. Expression of IL-17E is elevated in a number of Th2-driven diseases (Table 3).[64,75] Intranasal instillation of mice with IL-17E caused asthma-like symptoms, including up-regulation of IL-4/5/13, eosinophil infiltration and mucous production in the lung, and airway hyperresponsiveness, while treatment with anti-IL-17E blocking antibody prevented acute asthmatic symptoms in a mouse model of lung inflammation.[31,76] Interestingly, mice lacking IL-4/5/9/13 still displayed asthmatic symptoms upon intranasal injection of IL-17E, suggesting that IL-17E has a unique pathway bypassing conventional Th2 cytokines.[76]

Intriguingly, multiple studies suggest that the IL-17E pathway dampens Th1 and Th17 responses. Immunization of *il17e*$^{-/-}$ with myelin oligodendrocyte glycoprotein (MOG) peptide augments both IL-17A expression and EAE clinical scores, whereas administration of IL-17E to MOG-treated mice ameliorated disease.[77,78] Mechanistically, the

effect of IL-17E on disease is linked to expression of IL-23 and IL-13. In the absence of IL-17E signals, IL-23, a critical mediator of Th17 cell survival and maintenance, is elevated, whereas the reduction in disease severity seen with IL-17E treatment is linked to increased expression of IL-13, which in turn blocks IL-23 secretion by dendritic cells, preventing Th17 cell survival.[77,78] Similarly, IL-17E inhibited Th1 cell-driven colitis through blockade of IL-12 and IL-23 expression by $CD14^+$ cells isolated from the inflamed gut of patients with IBD.[79] These studies together with the observation that IL-17E expression is down-regulated in the inflamed colon tissue of patients with Crohn's disease or ulcerative colitis, suggest the possible use of IL-17E as a therapeutic agent for IBD.[79]

IL-17B, IL-17C and IL-17D

The cellular source(s), receptor utilization and target cells of the IL-17B, IL-17C and IL-17D family members are poorly characterized. Initially discovered using database searches for homology to IL-17A, it is unclear whether these cytokines share similar biological properties (Fig. 1).[80–82] Based on sequence comparison to IL-17A it is hypothesized that these family members also form dimers, although biochemical analysis of IL-17B suggests that it forms a tightly associated, non-disulphide linked dimer, which is in contrast to what is observed with IL-17A and IL-17F.[82] How IL-17C and IL-17D behave is undetermined. Although a specific high-affinity interaction was observed between IL-17B and the IL-17RB subunit using *in vitro* biochemical assays, the import of this finding is unclear.[82] Likewise, while IL-17C has been reported to associate with IL-17RE, the functional significance of this interaction has not been demonstrated.[7] The receptors for IL-17D are unknown.

Expression profiling has provided some information on the cellular sources of these cytokines (Table 1). Expression of IL-17B protein has only been reported in neurons and chondrocytes.[81–86] Interleukin-1β treatment of bovine cartilage explants promoted secretion of IL-17B,[87] suggesting that expression is modulated by pro-inflammatory stimuli. Similarly, although basal IL-17C mRNA is undetectable, significant induction is observed after exposure to inflammatory signals.[81] Tumour necrosis factor-α stimulated IL-17C secretion from human keratinocytes, whereas the TLR5 agonist, flagellin, promoted *il17c* mRNA expression in murine colon tissues.[9,88] Details of IL-17D protein expression have been reported.[80]

Pre-clinical and clinical studies suggest that expression of these family members is modulated by inflammation. Both IL-17B and IL-17C were detected in the paws of mice afflicted with collagen-induced arthritis, with IL-17B exclusively found in chondrocytes while IL-17C was detected in several populations of leucocytes.[89] Interleukin-17C was detected in lung and skin tissues following *Mycoplasma pneumoniae* and *S. aureus* infections, respectively.[90,91] Furthermore, IL-17C was detected in lesional psoriatic skin, but expression of IL-17B and IL-17D was depressed (Table 3).[9] It remains to be determined whether the regulated expression of these family members during inflammations contributes to the pathogenesis of inflammatory diseases.

A number of studies suggest that these family members may participate in host defence mechanisms. Pro-inflammatory cytokines, including TNF-α and IL-1β, were detected in a number of target cells, including monocytes, fibroblasts and cells from the peritoneal cavity, upon stimulation with IL-17B.[81,89] Interleukin-17C induced comparable responses in monocytes and fibroblasts.[81,89] Additionally, human subepithelial myofibroblasts treated with IL-17B, IL-17C or IL-17D weakly increased IL-6, IL-8, leukemia inhibitory factor, and matrix metalloproteinase 3 secretion.[92] Similar results were observed in IL-17D-stimulated human endothelial cells and chicken fibroblasts.[80,93] Inflammatory responses are also detected when IL-17B or IL-17C are over-expressed *in vivo*. Analogous to IL-17A, ectopic expression of IL-17B or IL-17C promoted neutrophil mobilization.[31,82] Bone marrow chimeric mice over-expressing IL-17B or IL-17C developed more severe collagen-induced arthritis, and displayed elevated expression of pro-inflammatory cytokines.[89] The adoptive transfer of $CD4^+$ T cells transduced with IL-17B or IL-17C into collagen-immunized mice also exacerbated disease, while blocking treatment with an anti-IL-17B blocking antibody inhibited the progression of arthritis and bone destruction in the collagen-induced arthritis model.[89] Overall, data from both human and animal models suggest that IL-17B, IL-17C and IL-17D might have a role in inflammatory disease, which highlights the need to further investigate their biological functions.

IL-17 receptors

The IL-17 receptor family represent a unique group of proteins that share minimal structural homology and signal transduction properties with other receptors.[7] Each chain is composed of a single transmembrane domain, an extracellular-fibronectin III-like (FnIII) domain and an intracellular similar expression to FGF genes (SEF)/IL-17R (SEFIR) domain. Membrane-bound and soluble versions of the receptors have been described, the latter resulting from alternative splicing events. While the SEFIR domain resembles the Toll-/IL-1R (TIR) domains found in receptors of the innate immune system, structural differences between the proteins preclude association of the SEFIR domains with signalling components of the TIR pathways. Upon ligand binding, the SEFIR domains within the IL-17 receptors associate with other SEFIR-containing proteins to initiate signalling cascades. As the

signalling properties of this family were recently covered in depth review, we will not be discussing this in further detail, and will focus on the functional consequences of these biochemical pathways.[7]

IL-17RA

Interleukin-17RA was first identified as the receptor for IL-17A; however, subsequent studies have demonstrated interaction with other family members. Although ubiquitously expressed, the major focus of IL-17RA biology has concentrated on stromal cells, which are the critical targets for IL-17A and IL-17F (Table 2). The regulation of IL-17RA expression is not well studied but elevated IL-17RA expression has been detected in human inflammatory diseases such as arthritic joints from patients with RA, suggesting a role in autoimmunity.[94,95] In accord with these reports, risk haplotypes within the IL-17RA gene that increase susceptibility to Crohn's disease have been identified by genetic studies.[96]

As discussed above, IL-17A and IL-17F require the IL-17RA–IL-17RC complex for function. The absence of either chain prevents cytokine-mediated pro-inflammatory cytokine secretion.[95] Biochemical measurements revealed that the affinity between IL-17A and IL-17RA was higher than that between IL-17RA and IL-17F, which may explain the discrepancy between the potency of IL-17A and IL-17F dimers.[6,11,97]

Structural analyses suggest that IL-17RA is a common chain for a number of IL-17 family members. Whereas the loss of IL-17RA inhibits IL-17E function, a requirement for this chain in IL-17B, IL-17C and IL-17D responses has not been demonstrated.[66,71,74,98]

A critical role for IL-17RA in host defence has been demonstrated using genetically deficient mice and blocking reagents. Neutrophil recruitment and granulopoiesis are impaired in *il17ra*$^{-/-}$ mice rendering them susceptible to microbial infections.[36,37,99–101] The inability to mount efficient immune responses protects these mice from developing disease in pre-clinical models of arthritis, IBD and influenza infection.[100,102,103] Likewise, soluble versions of IL-17RA confer protection from allograft rejection, joint-damage in models of arthritis and *Chlamydia* infection.[104–106] However, given the emerging data demonstrating the importance of IL-17RA in other cytokines, it is difficult to conclude that the effects of this reagent are solely the result of inhibition of IL-17A and IL-17F.[66] Further studies are required to evaluate this molecule *in vivo*.

IL-17RB

The IL-17RB chain was identified through screening of expressed sequence tag databases for IL-17RA-like molecules. As described above, both IL-17B and IL-17E bind to IL-17RB *in vitro*.[61,82] Expression of IL-17RB is detected in lung, kidney, bone and fetal liver tissues.[82] Interleukin-17RB is detected on multiple cell types and receptor expression is augmented by inflammatory signals (Table 2). Cross-linking the T-cell receptor, addition of the IL-7/15 cytokines, or co-culturing with dendritic cells stimulated with thymic stromal lymphoprotein, augment IL-17RB expression in memory Th2 cells.[64] Likewise, the addition of IL-33 and/or IL-17E enhances IL-17RB expression on the ckit^{+} lin^{-} cells, suggesting that receptor expression is partly regulated by an autocrine feedback loop.[71] As described above, the IL-17RA–IL-17RB complex is required for IL-17E activity. The IL-17E-mediated Th2 responses are inhibited in the absence of either chain.[71,74,98] In agreement with the pre-clinical data signifying a role in Th2 biology, elevated expression of IL-17RB is detected in human asthmatic lung tissue, and the 5661G-A polymorphism within the *IL-17RB* gene, has been identified to be protective against asthma.[64,107]

IL-17RC

Database mining for proteins homologous to IL-17RA led to the identification of IL-17RC.[97] Biochemical analyses demonstrate high-affinity interactions between IL-17RC–IL-17A and IL-17RC–IL-17F.[66] There have been no reports of IL-17RC binding to other IL-17 family members. Similar to IL-17RA, IL-17RC expression is elevated in patients with RA, emphasizing the role of this pathway in autoimmune disease pathology.[94,95] Intriguingly, alternative splice variants of IL-17RC have been detected in prostrate cancer tumours, but the function of these proteins is unclear.[108,109]

The function of IL-17RC has only been reported in the context of IL-17A and IL-17F biology. In agreement with the essential role for IL-17RC in IL-17A and IL-17F responses, genetic deletion or antibody-mediated blockade of this chain abrogates IL-17A and IL-17F responses such as pro-inflammatory cytokine induction.[11,110] Similar to the *il17ra*$^{-/-}$ mice, *il17rc*$^{-/-}$mice display delayed onset and milder disease in the MOG-EAE model, and increased susceptibility to fungal infections.[111,112]

IL-17RD and IL-17RE

The biology of these IL-17R family members, which were also identified through database searches, is unknown. Interleukin-17RD was detected in endothelial cells and epithelial cells (Table 2).[113] Similar to IL-17RB and IL-17RC, IL-17RD has also been demonstrated to co-localize and complex with IL-17RA.[114] Biochemical data suggest that this interaction mediates IL-17A function, as mutations within the cytoplasmic domain of IL-17RD prevent IL-17A induction of the 24p3 luciferase reporter.[114] Other studies suggest that this receptor may have

inhibitory effects, as over-expression suppresses fibroblast growth factor-mediated Ras and phosphatidyl inositol 3-kinase signalling. The significance of IL-17RD *in vivo* remains to be determined.

Likewise, the biology of IL-17RE is undetermined. It has been reported that IL-17C binds to IL-17RE, although the import of this interaction is not understood.[7] The specific cellular populations that are IL-17RE$^+$ have not been defined.[115] Although multiple splice variants of the IL-17RE gene have been identified, the biological significance of these isoforms is unknown.[115] A role in MAPK activation has been detected, but further studies are required to understand the significance of this observation.

Conclusions and future directions

Although substantial efforts have elucidated the biological functions of this unique family, there is still much to be discovered. In particular, the significance of the newer family members in host defence and inflammation needs to be addressed. Understanding how these proteins modulate inflammation in the disease setting will be beneficial for development of new therapies.

Disclosures

The authors declare no conflicts of interest.

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